Section: Obstetrics and Gynecology

Original Research Article

CLINICOPATHOLOGICAL STUDY OF ABNORMAL UTERINE BLEEDING IN PERIMENOPAUSAL WOMEN

Jahnavi Anne[1], D. Suchetha[2], Divya Daniel[3], G Mahalakshmi[4]

[1]*Post Graduate, Department of Obstetrics and Gynecology, Gandhi Medical College/Hospital, Secunderabad, Telangana, India.*
[2]*Associate Professor, Department of Obstetrics and Gynecology, Gandhi Medical College/Hospital, Secunderabad, Telangana, India.*
[3]*Assistant Professor, Department of Obstetrics and Gynecology, Gandhi Medical College/ Hospital, Secunderabad, Telangana, India.*
[4]*Professor, Department of Obstetrics and Gynecology, Gandhi Medical College/Hospital, Secunderabad, Telangana, India.*

Received *: 07/04/2025*
Received in revised form *: 20/05/2025*
Accepted *: 13/06/2025*

Corresponding Author:
Dr. D Suchetha,
Associate Professor, Department of Obstetrics and Gynecology, Gandhi Medical College/Hospital, Secunderabad, Telangana, India.
Email: drsuchetambbsmd@gmail.com

DOI: 10.70034/ijmedph.2025.2.466

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (2); 2574-2580

ABSTRACT

Background: The aim is to determine the causes of abnormal uterine bleeding in perimenopausal women.

Materials and Methods: This is a Prospective observational study conducted for a period of one year in 170 women with menstrual complaints who were admitted to the gynaecology department. All women in the perimenopausal age {>/= 40 years} who presented with AUB to the gynaecology clinics were included in the study and women <40 years of age, postmenopausal women (menopause status >1year) were excluded from the study.

Results: Total study population was 170, mean age of the study population was 44.29 ∓ 3.2 years. Post-surgery HPE showed leiomyoma in 55 women (36.7%), hyperplasia without atypia in 30 (20%) and proliferative endometrium in 22 women (14.7%) as majority of cases in descending order. The statistical analysis revealed a substantial correlation ($P < 0.05$) between the clinical and pathological diagnoses.

Conclusion: The pipelle sampling is a new office based procedure which is equally effective as endometrial curetting. The patients that were categorised using the PALM-COEIN system showed a strong association between clinicopathology and the original diagnosis.

Keywords: Abnormal Uterine Bleeding, Histopathological Examination, Leiomyoma, Pipelle sampling.

INTRODUCTION

Uterine bleeding is a natural physiological occurrence that exhibits significant variability among women. Menstruation, a physiological process in females, involves the shedding of the secretory endometrium. This shedding is accompanied by uterine bleeding and typically happens regularly if it is an ovulatory cycle. The range of diversity in menstrual bleeding is extensive, making the detection of pathology a challenging task. The aetiology of abnormal uterine bleeding exhibits variability, resulting in diverse patterns of bleeding. The bleeding pattern might occasionally provide valuable diagnostic information regarding the underlying cause.[1]

The objective of management will be contingent upon the etiological diagnosis. The comprehensive evaluation of a patient's medical history, physical examination, and pelvic examination plays a crucial role in identifying and localizing the origin and cause of bleeding. The data obtained from this study will provide indications for additional studies such as ultrasonography and histology. Histopathology of endometrium can be done either by pipelle or endometrial curettage. Ultrasound imaging provides valuable insights into the current condition of the uterus and ovaries. Additional diagnostic procedures such as magnetic resonance imaging (MRI) and computed tomography (CT) scans may be conducted if necessary and can provide valuable assistance. These factors also assist in the process of disease staging in case of malignancy. Additionally, there has been a recent emergence of hysteroscopic visualisation of the uterine cavity, which serves as a novel diagnostic tool.[1]

Abnormal uterine bleeding is a prevalent concern encountered in gynaecological outpatient departments, posing significant challenges for gynaecologists. Abnormal uterine bleeding refers to

any variation in the frequency of menstrual cycle, duration of bleeding, amount of blood loss, or a combination thereof. It is commonly observed across a broad age range, spanning from the onset of adolescence till the perimenopausal period. The perimenopausal phase is frequently observed as the most prevalent age range.

A diverse range of anatomical and functional factors might contribute to the occurrence of abnormal uterine bleeding. Frequently encountered structural aetiologies encompass fibroids, polyps, adenomyosis, or neoplasia. The most prominent category consists of functional disturbances, commonly known as AUB-O. Abnormal uterine bleeding due to ovulatory dysfunction is characterized as abnormal uterine bleeding that cannot be attributed to identifiable organic factors, difficulties related to pregnancy, or systemic ailments.[2] The primary objective of this study is to investigate the histopathological characteristics of the endometrium/myometrium in women experiencing abnormal uterine bleeding during the perimenopausal phase.

MATERIALS AND METHODS

The present study is a prospective study of 170 Patients from gynaecological outpatient Department at Gandhi Medical College, Secunderabad presenting with menstrual complaints. The study materials were collected from endometrial samples (endometrial curettage, pipelle) and hysterectomy, myomectomy, hysteroscopic specimens of the patients who presented with abnormal uterine bleeding. The specimens were fixed with 10% formalin followed by routine processing. The paraffin blocks were cut and stained with routine Haematoxylin and Eosin stains.

Sample Size: 170

Duration of Study: July 2022 to December 2023

Inclusion Criteria

All women in the perimenopausal (>40 years) who presented with AUB to the gynaecology clinics.

Exclusion Criteria

Women < 40 years of age, Postmenopausal women (menopause status >1 year), Cases were selected by diagnosis on History, General Physical Examination, Abdomen and Pelvic Examination and Routine investigations.

Proforma specially made for the study was used. The age, parity, menstrual complaints will be noted and clinical diagnosis with ultrasound report and histopathological reports (of endometrial tissue.) were analysed. The study materials will be collected from endometrial samples and post-surgery (hysterectomy, myomectomy, polypectomy) specimens of the patients who presented with abnormal uterine bleeding.

RESULTS

Table 1: Demographic distribution in study.

Age(years)	Number(n)	%
40	17	10.0
41	17	10.0
42	17	10.0
43	19	11.2
44	13	7.6
45	11	6.5
46	11	6.5
47	15	8.8
48	22	12.9
49	13	7.6
50	15	8.8
Grand Total	170	100.0
Parity		
0	12	7.1
1	31	18.2
2	35	20.6
3	34	20.0
4	37	21.8
5	21	12.4
Predominant Symptom		
Menorrhagia	94	55.3
Metrorrhagia	7	4.1
Polymenorrhagia	69	40.6
Hb(g/dl)		
<7	33	19.4
7-8.9	64	37.4
9-10.9	49	28.8
>/=11	24	14.1

The mean age of the study population was 44.29 ∓ 3.2 years. Majority (21.8%) were parity 4. Majority had menorrhagia (55.3%) as predominant symptom. The mean Hb was 8.5gm% Almost 86% patients had some degree of anaemia.

Table 2: Clinical diagnosis according to Palm-coein.

Clinical diagnosis	Number(n)	%
Adenomyosis	18	10.6
Endometrial	2	1.2
Hyperplasia	11	6.5
Iatrogenic	2	1.2
Leiomyoma	47	27.6
Malignancy	1	0.6
Not specified	1	0.6
Ovulatory	78	45.9
Polyp	10	5.9
Grand Total	170	100.0

Table 3: USG and Endometrial sampling method

USG diagnosis	Number(n)	%
Adenomyosis	18	10.6
Bulky	37	21.8
Leiomyoma	46	27.1
Normal	60	35.3
Polyp	9	5.3
Sampling method		
Dilatation & curettage	96	56.5
Pipelle	74	43.5
Endometrial sampling HPE report		
benign endometrial polyp	5	2.9
endometroid cancer	2	1.2
hyperplasia with atypia	3	1.8
hyperplasia without atypia	16	9.4
Secretory phase	19	11.2
Proliferative phase	122	71.8
Inconclusive	3	1.7

Dilatation and curettage was done in 96 (56.5%) out of 170 women. 29

Table 4: Medical Management

Medical management	Number(n)	%
not used	42	24.7
used	128	75.3
Duration of medical management (months)		
2	11	8.6
3	113	88.3
4	4	3.1
Response to medical management		
not responded	108	84.4
responded	20	15.6

128 patients out of 170 underwent medical management. 2 patients who were not fit for medical management were directly taken up for surgery following endometrial sampling report as indicated. In 128 out of 170 patients who underent medical management majority (88.3%) of them used medical management for about 3 months. Amongst 170 patients included in the study, 128 underwent medical management. Amid those 128 patients, 20 patients (15.6%) responded to medical management and rest were proceeded for surgery.

Table 5: Procedure Done

Surgical procedure done	Number(n)	%
Hysterectomy	128	85.3
hysteroscopic polypectomy	8	5.4
Myomectomy	12	8.0
radical hysterectomy	2	1.3
Grand Total	150	100.0

Total of 150 in 170 women had undergone surgical procedure either due to direct indication (42 women) or due to non-response to medical management (108 women).

Table 6: Post-surgery HPE report

HPE report	Count of HPE report	%
Adenomyosis	16	10.7
Benign endometrial polyp	9	6.0
Endometritis	3	2.0
Endometroid cancer	2	1.3

Hyperplasia with atypia	7	4.7
Hyperplasia without atypia	30	20.0
Leiomyoma	55	36.7
Proliferative phase	22	14.7
Secretory phase	6	4.0
Grand Total	150	100.0

The above table represents the histopathological findings of the 150 patients who underwent surgery.

Table 7: USG versus post surgery HPE diagnosis

	USG					
HPE report	**Adenomyosis**	**Bulky**	**Leiomyoma**	**Normal**	**Polyp**	**Grand total**
Adenomyosis	15	1				16
Polyp		1		2	6	9
Endometritis				2	1	3
endometroid cancer		1		1		2
hyperplasia with atypia		3	1	3		7
hyperplasia without atypia		12	2	15	1	30
leiomyoma	1	5	43	6		55
Proliferative phase		8		13	1	22
Secretory phase	2	2		2		6
Grand Total	18	33	46	44	9	150

Table 8: USG versus palm-coein diagnosis

PALM-COEIN diagnosis	**USG**					
	Adenomyosis	**Bulky**	**Leiomyoma**	**Normal**	**Polyp**	**Grand Total**
Adenomyosis	18					18
Endometrial				1	1	2
Hyperplasia		4	2	5		11
Iatrogenic		1		1		2
Leiomyoma			44	3		47
Malignancy		1				1
not specified				1		1
Ovulatory		30		48		78
Polyp		1		1	8	10
Grand Total	18	37	46	60	9	170

Table 9: Palm-coein versus post surgery HPE diagnosis post surgery HPE

Palm coein										
	Adenomyosis	**Polyp**	**endometritis**	**Endometroid cancer**	**Hyperplasia with atypia**	**Hyperplasia without atypia**	**leiomyoma**	**proliferative**	**Secretory**	**Grand total**
Adenomyosis	15						1		2	18
Endometrial			1					1		2
Hyperplasia				1	1	9				11
Iatrogenic			1						1	2
Leiomyoma					1		46			47
Malignancy				1						1
Not specified						1				1
ovulatory	1	2			5	19	8	20	3	58
polyp		7	1			1		1		10
Grand total	16	9	3	2	7	30	55	22	6	150

Women were classified into PALM COEIN based on clinical history, radiological findings and endometrial biopsy report.

PALM COEIN diagnosis was compared to the post surgery HPE in the above table.

1. Leiomyoma: Sensitivity= 90.48% Specificity = 98.45% PPV= 90.48% NPV= 98.45%
2. Polyp: Sensitivity= 73.68% Specificity = 100% PPV= 100%
NPV= 96.32% NPV= 96.18%
3. Adenomyosis: Sensitivity= 78.26% Specificity = 99.21% PPV= 94.74% NPV= 96.18%

DISCUSSION

Among the most prevalent and difficult cases seen by gynaecologists is abnormal uterine bleeding. Up to a third of all gynaecological outpatient visits are caused by it. This might potentially impair a person's social, emotional, and physical well-being in a way that diminishes their quality of life.

AUB occurs when the frequency, length, and volume of blood flow deviate from the typical monthly rhythm or from the pattern experienced following menopause. AUB can have a variety of anatomical

and functional causes. The investigation and management of AUB patients are enormously impacted by contentious and nonuniform terminology as well as by the absence of standardised methodologies for inquiry and etiological classification. In 2011, FIGO came up with a nomenclature and categorization system for AUB called PALM-COEIN to get over this problem.[3,4] Beginning in one's early forties, perimenopause is characterised by a gradual decline in ovarian function and can continue for up to two years following the last menstrual period (LMP).

Although the relative importance of the PALM-COEIN categories in AUB varies with age, fibroids and endometrial polyps continue to be the most prevalent structural causes of AUB throughout perimenopause. Myomas and adenomyosis, which are causes of AUB, become more noticeable in the 40s and 50s.[5] It is worth mentioning that the occurrence of structural disorders such as fibroids, polyps, and adenomyosis, as well as their coexistence or presence of uterine cancer, tends to rise with age as well.

Uterine haemorrhage can also be caused by hormonal or non-hormonal drugs, some systemic or local diseases, and certain treatments (e.g., tamoxifen, oral anticoagulants). Perimenopausal women often experience AUB due to hematologic dysfunctions. For example, a significant portion of women with von Willebrand factor deficiency (affecting 0.5-1% of the population), platelet dysfunction and rare factor deficiencies report AUB as their primary symptom.[6]

Treatment of AUB includes medical management and surgical management. Conservative medical management includes progestogens, GnRH agonists and antagonists, mifepristone, depot medroxyprogesterone injections and levonorgestrel intrauterine devices.[7] For many women, conservative medical management may be unsuccessful, or may be associated with significant side effects. Surgical management of AUB may include procedures that destroy the endometrium (endometrial ablation), uterine preserving surgery (myomectomy, polypectomy) or hysterectomy.

Hysterectomy, despite the above measures, ultimately is chosen by more than half of women with HMB within 5 years of their referral to gynaecologist.[7] Nonetheless, hysterectomy-alternative uterus-preserving therapies have emerged throughout the last 30 years. Alternatives to hysterectomy for benign AUB include minimally invasive procedures such as hysteroscopic polypectomy, myomectomy, endometrial resection/endometrial ablation, or uterine artery embolization. Although hysteroscopic therapies are well-received by patients and can temporarily enhance their quality of life, they do not completely remove the possibility of AUB recurrence or the necessity for further intervention.

Because it definitively establishes a diagnosis and directs the appropriate course of treatment, histological evaluation continues to serve as the foundation of present practise for patients of AUB. Hormonal imbalance pattern, atrophic endometrium, endometritis, polyps, hyperplasia, and carcinoma are among the most common pathologies that can be discovered histologically in AUB. Other common pathologies include non-secretory endometrium with stromal and glandular breakdown, luteal phase defect, pill effect, and disorderly proliferative endometrium.[8]

The mean age of the study population was 44.29 ∓ 3.2 years. The mean age was 41 years with 56% of study population belonging to 41-50 years in a study by Singh et al.[9] The mean age was 45 years with 54% of the population between 41-45 years in Katuwal et al study,[10] most common age group was 41-44 years (30%) followed by 45-49 years (27.5%). The mean age of Abid et al,[11] study was 40 years. comparing the mean age distribution of the study population in various studies done on AUB, published in the literature to the mean age in the present study. Comparing the mean age distribution of the study population in assorted studies done on AUB, published in the literature to the mean age in the present study.

Majority had menorrhagia (55.3%) as the predominant symptom in the present study. The majority of patients (41.7%) presented with menorrhagia in Katuwal et al study.[10] Polymenorrhea (30%) was commonly seen as a presenting symptom in a study by Abid et al.[11] 44% had menorrhagia in Acharya et al study.[12] Comparing the menorrhagia (%) as the predominant symptom of the study population in various studies done on AUB, published in the literature to the percentage in the present study.

Clinical diagnosis according to PALM-COEIN: In the present study, AUB -P comprises of 5.9%. In Sun et al,[13] study AUB P was 16.2% and in Abid et al,[11] study the endometrial polyps were observed in 14% of the cases. Patients risk factors include increasing age, obesity, tamoxifen use. They usually have no symptoms, although some may present with heavy menstrual bleeding or intermenstrual bleeding. Polyps are not considered a significant risk factor for the development of carcinoma. Comparing the AUB -P (%) of the study population in various studies done on AUB, published in the literature to the percentage in the present study.

In the present study, AUB -A comprises of 10.6%.In Sun et al study,[14] AUB A was 4.9% and in Tapkan et al,[14] study Adenomyosis was observed in 11.8% of the cases, In Karena et al study,[15] AUB – A was 30%. Comparing the AUB -A (%) of the study population in various studies done on AUB, published in the literature to the percentage in the present study.

AUB -L was observed in 27.6% of the population in the present study. It was 28% in Tapkan et al study,[14] 45% in Karena et al study,[15] 36% in Singh et al,[9] 19% in Sudhamani et al.[16] In most of the studies, Leiomyoma was the most common. These are benign smooth muscle neoplasms usually originating from

the myometrium. Based on their location, they may be categorised into two subclasses: submucosal (L-SM) and other (L-O). Most women are usually asymptomatic, however heavy menstrual bleeding (HMB) is more commonly caused by submucosal fibroids, which are believed to disrupt the uterine cavity. Comparing the AUB -L (%) of the study population in various studies done on AUB, published in the literature to the percentage in the present study.

AUB – M was noticed in 7.1% of the study population in the present study. This includes Malignancy and hyperplasia. Most endometrial cancers arise following progression of histologically distinguishable hyperplastic lesions. Abid et al,[11] observed that among the 241 patients in their study, 5% had endometrial hyperplasia amongst whom 7 people had hyperplasia with atypia. The most common age group to experience hyperplasia with atypia was those who had gone through menopause (46%), followed by those in the perimenopausal stage (38.5%) and the reproductive age group (15.5%). In Sudhamani et al study,[16] 23% had AUB-M (17% hyperplasia and 6% malignant tumours. Endometrioid carcinoma accounted for 23% of those cases, and the incidence rate was 1.3% (4/300) in Singh et al study.[9] AUB – C was observed in 0% of the study population in the present study. It was 0.3% in Karena et al study.[15]

In the present study, AUB -O comprises of 45.9%. Sun et al,[13] study based on their results showed that AUB in Chinese women is in general caused by non-structural factors, with AUB-O being the most common kind (57.7%). For individuals with AUB-O, the bleeding episodes are usually variable. Amenorrhea, HMB and intermenstrual bleeding often interchange. Ovulation and subsequent endometrial stability are not achieved because the hypothalamic-pituitary-ovarian axis does not produce the required hormonal feedback.

Ovulatory disorders were seen in 22% of the study population in Karena et al study.[15]

In the present study, AUB -I comprises of 1.2% and AUB – E was 1.2%. As per the post-surgery HPE report of the 150 patients who underwent surgery 36.7% of the cases showed leiomyoma, 20% hyperplasia without atypia, 14.7% proliferative endometrium, 10.7% adenomyosis and 6% showed benign endometrial polyp. USG sensitivity and specificity in diagnosing Leiomyomas was 90.48% and 98.45% and for endometrial polyps it was 73.68% and 100%. USG sensitivity and specificity in diagnosing Adenomyosis was 78.26% and 99.21% in the present study. When comparing the TVS results with the HPE, Acharya et al,[12] found that 100% of cases had fibroid or hyperplasia with polyp, whereas 53.33% had hyperplasia alone, 88.19% had polyp, and 53.33% had normal findings. While hysteroscopy had an accuracy rate of 92% and a sensitivity rate of 82.05%, TVS had an accuracy rate of 72.73%, a positive predictive value (PPV) of 91.43%, a specificity rate of 53.33%, and a sensitivity rate of 80%.

In 236 out of 241 AUB subjects (98%, or 236/241), benign endometrial pathology was seen in Abid et al study.[11] The histopathological spectrum of AUB varies significantly between age groups. In cases with AUB, polymenorrhea was the most prevalent symptom. Hormonal imbalance was the most prevalent pathology. Endometrial hyperplasia and endometrial cancer, two lesions that tend to advance more rapidly with age, are more common in women in their perimenopausal and postmenopausal years. Still, after menopause, endometrial polyps were the most prevalent kind of pathology.

Singh et al,[9] observed the total incidence of AUB was 30.0% due to leiomyoma and 29.66% due to adenomyosis. A high incidence of concordance (85.03%) was observed between clinicopathological findings and hysterectomy procedures. There was a statistically significant agreement between clinical and pathological diagnoses in positive cases ($P < 0.05$).

CONCLUSION

Excessive menstrual blood loss is a common reason for women to seek medical help. Abnormal uterine bleeding due to ovulatory dysfunction (AUB-O) is found to be the most common cause of menstrual abnormality in perimenopausal women. Leiomyoma (AUB-L) was the most common structural cause of abnormal uterine bleeding in this group. Menorrhagia is a common symptom at presentation. Evaluation of abnormal uterine bleeding in perimenopausal women help in diagnosis of malignancy and premalignant condition like hyperplasia in early stage. The pipelle sampling is a new office based procedure which is equally effective as endometrial curetting.

The patients that were categorised using the PALM-COEIN system showed a strong association between clinicopathology and the original diagnosis.

Additionally, the approach allows for the clinical and histological evaluation of several aetiologies that may contribute to AUB. Cases without particular symptoms might be overlooked clinically, in such cases histology is crucial for making an accurate diagnosis.

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